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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,094	12/31/2003	Gautam Vinod Daftary	B2351010.1	6940

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,094	DAFTARY ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,12 and 14-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,12 and 14-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The RCE dated 11-26-08 is acknowledged.

Claims included in the prosecution are 1-8, 10, 12 and 14-22.

To reduce the issues, the rejections involving Hong reference are withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-8, 10, 12 and 14-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to claim 1, the solvent or mixture of solvents is removed before or ***after hydrating the lipids***. If the aqueous medium is added when the lipids are in a solution form in a mixture of organic solvents, it is unclear to the examiner as to how one can hydrate the lipids. 'Extraliposomal hydration salt' on line 10 of claim 1 has no antecedent basis. Also unclear as to how one can remove the extra liposomal salt by simply using a sucrose-histidine buffer. Do applicants mean by employing dialysis? If so, the examiner suggests restructuring the claim by reciting this limitation.

It is unclear at what step the therapeutic agent is loaded as recited in claim 3.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-8, 10, 12, 14-22 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kirpotin (6,110,491) in view of Wong (US 2005/0025822), Mammarella (US 2006/0078605) individually or in combination further in combination with Papahadjopoulos (4,235,871).

Kirpotin discloses a method of preparation of liposomes by forming a lipid film and hydrating it with a buffer containing ammonium sulfate (Example 7). Kirpotin also teaches that if necessary, to achieve an osmolarity of 377 mmole/kg, sucrose could be added to the medium (Example 8). The liposomes contain hydrogenated egg phospholipid and cholesterol. Doxorubicin is loaded into the preformed liposomes (Example 7). Although in the examples Kirpotin uses PEG-phospholipids, on col. 9, lines 22-33 teaches either the naturally occurring or synthetic phospholipids which implies that the use of PEG-phospholipids for the method of preparation of liposomes is not necessary. What is lacking in Kirpotin is the teaching of the amount of aqueous medium added to per mol phospholipid. However, since the final product in Kirpotin is a liposome just as in instant case and since complete hydration of the phospholipid is required for the formation of the liposomes, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results. Kirpotin lacks the teaching of the teachings of the removal of ammonium sulfate from the external medium using a

sucrose-histidine buffer solution. As pointed out above, Kirpotin's method involves removal of the organic solvent before the hydration and not after. Instant claims recite two alternatives.

Wong while disclosing a method of making liposomal formulations teaches the removal external ammonium sulfate using sucrose in a buffer and the final liposomal preparation has 10 mM histidine and 10 % sucrose buffer (0063).

Mammarella while disclosing a method of making liposomal formulations teaches the removal external ammonium sulfate using sucrose in a buffer and the final liposomal preparation has 0.15 % histidine and 10 % sucrose buffer (0045-0048, 0066 and 0067).

Papahadjopoulos discloses methods of formation of liposomes. The methods involve either removal of the organic solvent before hydration (Example 1) or making an emulsion using an organic solvent containing phospholipid and an aqueous medium and evaporating the organic solvent (Example 2). In either method, the amount of the lipid is 100 micromoles and the aqueous medium added is 1.5 ml which corresponds to 15 ml of aqueous medium per millimole of the phospholipid and the hydration medium contains histidine.

It would have been obvious to one of ordinary skill in the art to remove the extraliposomal salt using sucrose-histidine buffer instead of sucrose-butter taught by Forssen with a reasonable expectation of success since Wong and Mammarella teach that the final preparations of liposomes could be in sucrose-histidine buffer. Although neither Kirpotin and Wong teach the exact amount of the hydrating medium, However, since complete hydration of the phospholipid is required for the formation of the

liposomes, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results. Making an emulsion of the phospholipid containing organic solvent and an aqueous medium in the ratios of 1 millimole of lipid/15ml of aqueous medium and removing the organic solvent to form liposomes would have been obvious to one of ordinary skill in the art since Papahadjopoulos teaches that liposomes can be produced by either process.

Applicant's arguments have been fully considered, but are not deemed to be moot in view of the new rejection. However, the examiner would address applicant's arguments pertaining to Kirpotin. Applicant's arguments based on KSR decision are not persuasive since the examiner has provided sufficient reason and motivation to combine and the reasonable expectation of success.

Applicant argues that Kirpotin is concerned with liposome loading and does not teach about a process for making long-circulating non-PEGylated liposome. This argument is not persuasive since instant claims are method claims and not method of increasing the circulation time of the liposomes. Prior art teaches similar method. Applicant points out to col. 14, lines 40-42 and argues that Kirpotin teaches away from using ammonium ions. At this location Kirpotin states that doxorubicin at this temperature does not form a precipitate. How can this be considered as teaching away. Applicant argues that Example 7 and 8 thus show that the use of ammonium sulfate in the hydrating medium in a PEGylated liposome is not useful for entrapping drug in the desired amounts and that the office action has not provided an explanation as to how

this in any way teaches, suggests or motivates one skilled in the art to use ammonium sulfate in the hydrating medium by hydrating non-PEGylated phospholipids. Applicant further argues that Kirpotin does not teach instantly clamed phospholipids. These arguments are not persuasive. First of all, instant claims do not recite any specific drug amounts. As pointed out before, although in the examples Kirpotin uses PEG-phospholipids, on col. 9, lines 22-33 teaches either the naturally occurring or synthetic phospholipids which implies that the use of PEG-phospholipids for the method of preparation of liposomes is not necessary. The term, synthetic implies even claimed phospholipids. Applicant further argues based on the declaration by MR. Annappa that instant invention provides unexpected results compared to the PEGylated liposomal preparation (CAELYX) marketed currently. These arguments are not persuasive since the proper comparison to show unexpected results would be the comparison with Kirpotin and not with the commercially available PEGylated product since this product was not used in the rejection. Instant claims recite a process of preparation of liposomes containing phospholipids and sterol, which are not PEGylated and Kirpotin, teaches the preparation of non-PEGylated liposomes. Furthermore, instant claims are drawn to a process of preparation and the product formed and not drawn to method of increasing the circulation time of the liposomes. The examiner thus, has not merely dismissed the declarations.

5. Claims 1-8, 10, 12, 14-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong (Clinical Cancer Research, 1999) of record in view of Wong (US 2005/0025822), Mammarella (US 2006/0078605) individually or in combination Papahadjopoulos (4,235,871) and Janoff (4,880,635).

Hong teaches a method of preparation of doxorubicin loaded liposomes. The method involves hydration of the lipids using ammonium sulfate solution (abstract and Materials and Methods). What are lacking in Hong are the use of sucrose in the hydration buffer and the removal of external ammonium sulfate. It is unclear from Hong as to how much hydration buffer is added. Hong's method involves removal of the organic solvent before the hydration and not after. Instant claims recite two alternatives.

Wong while disclosing a method of making liposomal formulations teaches the removal external ammonium sulfate using sucrose in a buffer and the final liposomal preparation has 10 mM histidine and 10 % sucrose buffer (0063).

Mammarella while disclosing a method of making liposomal formulations teaches the removal external ammonium sulfate using sucrose in a buffer and the final liposomal preparation has 0.15 % histidine and 10 % sucrose buffer (0045-0048, 0066 and 0067).

Papahadjopoulos discloses methods of formation of liposomes. The methods involve either removal of the organic solvent before hydration (Example 1) or making an emulsion using an organic solvent containing phospholipid and an aqueous medium and evaporating the organic solvent (Example 2). In either method, the amount of the lipid is 100 micromoles and the aqueous medium added is 1.5 ml which corresponds to 15 ml of aqueous medium per millimole of the phospholipid.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (Example 1; col. 21, line 23 through col. 21, line 27). Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole).

It would have been obvious to one of ordinary skill in the art to remove the extra liposomal salt using sucrose-histidine buffer instead of sucrose-butter taught by Forssen with a reasonable expectation of success since Wong and Mammarella teach that the final preparations of liposomes could be in sucrose-histidine buffer. Although neither Kirpotin and Wong teach the exact amount of the hydrating medium, However, since complete hydration of the phospholipid is required for the formation of the liposomes, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results.

Making an emulsion of the phospholipid containing organic solvent and an aqueous medium in the ratios of 1 millimole of lipid/15ml of aqueous medium and removing the organic solvent to form liposomes would have been obvious to one of ordinary skill in the art since Papahadjopoulos teaches that liposomes can be produced by either process. To include sucrose in the hydration medium of Forssen would have been obvious to one of ordinary skill in the art since such a procedure would enable the presence of sucrose within the liposomes as well as outside and since Janoff teaches that the liposomes retain the active agent during dehydration and rehydration procedures.

Although applicant's arguments are deemed to be moot, the examiner would address applicant's arguments with regard to Hong and Janoff. Applicant argues that Hong is directed to the preparation of both PEGylated liposomes. This argument is not persuasive since Hong teaches the preparation of both liposomal composition with and without PEG as the title in Hong itself states (see also Materials and Methods and Figures 1-4). Instant claims are method of preparation and product claims. The motivation to add ammonium sulfate and sucrose need not be the same as applicants. Applicant's arguments regarding Janoff re not persuasive since Janoff is added to show that the addition of claimed amounts of hydrating medium is known in the art. Furthermore, Janoff clearly teaches the dehydration of liposomes using protective sugar trehalose. This implies the protection of the sugar, sucrose (col. 5, line 60) during dehydration process of the liposomes (see also col. 7, lines 47-61).

6. Claims 1-8, 10, 12, 14-22 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong (Clinical Cancer Research, 1999) of record in view of Wong (US 2005/0025822), Mammarella (US 2006/0078605) individually or in combination Papahadjopoulos (4,235,871) and Janoff (4,880,635) and either Radhakrishnan (5,192,528) or Uchiyama cited above.

The teachings of Hong, Wong, Mammarella, Papahadjopoulos and Janoff have been discussed above.

Radhakrishnan while disclosing corticosteroid containing liposomes teaches that the aqueous medium is added to a final lipid concentration of between about 10 to 100

micromole/ml which translates to 100 to 10 ml per mmole phospholipid (abstract and col. 5, lines 15-29).

Uchiyama while disclosing a method of preparation of liposomes containing EPC, HEPC, DCP and cholesterol teaches the hydration of 200 micromoles of lipids using 5 ml of aqueous medium, which translates to 1 mmole lipid and 25 ml of aqueous medium (Materials and methods, liposome preparation).

One of ordinary skill in the art would be motivated to use claimed amounts for the hydration medium since the references of Radhakrishnan and Uchiyama show the routine use of claimed amounts for hydrating the phospholipids to form liposomes.

7. Claims 1-8, 10, 12, 14-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forssen (5,714,163) in combination with Wong (US 2005/0025822), Mammarella (US 2006/0078605) individually or in combination.

Instant claims recite two alternatives: the organic solvent is removed before or after the hydration. That means the hydration is performed on a dried lipid film or in a solution of the lipids in the organic solvent.

Forssen discloses a method of preparation of liposomes wherein the spray dried lipid mixture containing DSPC and cholesterol is hydrated with ammonium sulfate. Since it is a lipid mixture dissolving the lipids in an organic solvent for spray-drying is implicit (Example 1). Although Forssen teaches the use of 300 mM sucrose for hydration medium, he does not teach the use of hydration buffer containing both ammonium sulfate and sucrose. The liposomes are then subjected to buffer change using 300 mM sucrose.

What is lacking in Forssen is the use of sucrose-histidine buffer solution to remove the ammonium salt such that the final preparation has sucrose-histidine buffer.

Wong while disclosing a method of making liposomal formulations teaches the removal external ammonium sulfate using sucrose in a buffer and the final liposomal preparation has 10 mM histidine and 10 % sucrose buffer (0063).

Mammarella while disclosing a method of making liposomal formulations teaches the removal external ammonium sulfate using sucrose in a buffer and the final liposomal preparation has 0.15 % histidine and 10 % sucrose buffer (0045-0048, 0066 and 0067).

It would have been obvious to one of ordinary skill in the art to remove the extraliposomal salt using sucrose-histidine buffer instead of sucrose-butter taught by Forssen with a reasonable expectation of success since Wong and Mammarella teach that the final preparations of liposomes could be in sucrose-histidine buffer. Although neither Forssen and Wong teach the exact amount of the hydrating medium, However, since complete hydration of the phospholipid is required for the formation of the liposomes, in the absence of showing unexpected results, it is deemed obvious to one of ordinary skill in the art to vary the amounts of the hydrating medium to obtain the best possible results.

8. Claims 1-8, 10, 12, 14-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forssen (5,714,163) in combination with Wong (US 2005/0025822), Mammarella (US 2006/0078605) individually or in combination as set forth above, further in view of and either Radhakrishnan (5,192,528) or Uchiyama (International Journal of Pharmaceutics, 1995) or Papahadjopoulos (4,235,871) or Janoff (4,880,635)

The teachings of Forssen, Wong, and Mammarella have been discussed above. These references do not specifically disclose the claimed hydrating amounts of the aqueous medium.

Radhakrishnan while disclosing corticosteroid containing liposomes teaches that the aqueous medium is added to a final lipid concentration of between about 10 to 100 micromole/ml which translates to 100 to 10 ml per mmole phospholipid (abstract and col. 5, lines 15-29).

Uchiyama while disclosing a method of preparation of liposomes containing EPC, HEPC, DCP and cholesterol teaches the hydration of 200 micromoles of lipids using 5 ml of aqueous medium, which translates to 1 mmole lipid and 25 ml of aqueous medium (Materials and methods, liposome preparation).

Papahadjopoulos discloses methods of formation of liposomes. The methods involve either removal of the organic solvent before hydration (Example 1) or making an emulsion using an organic solvent containing phospholipid and an aqueous medium and evaporating the organic solvent (Example 2). In either method, the amount of the lipid is 100 micromoles and the aqueous medium added is 1.5 ml which corresponds to 15 ml of aqueous medium per millimole of the phospholipid.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (col. 21, line 23 through col. 21, line 27). Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole).

One of ordinary skill in the art would be motivated to use claimed amounts for the hydration medium since the references of Radhakrishnan, Uchiyama, Papahadjopoulos, Janoff show the routine use of claimed amounts for hydrating the phospholipids to form liposomes. .

9. Claims 1-8, 10, 12, 14-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forssen (5,714,163) in combination with Wong (US 2005/0025822), Mammarella (US 2006/0078605) individually or in combination as set forth above, further in view of and either Radhakrishnan (5,192,528) or Uchiyama (International Journal of Pharmaceutics, 1995) as set forth above, further in view of Kirpotin (6,110,491).

The teachings of Forssen, Wong, and Mammarella have been discussed above. These references do not teach the use of sucrose and ammonium sulfate together in the hydrating medium.

Kirpotin discloses a method of preparation of liposomes by forming a lipid film and hydrating it with a buffer containing ammonium sulfate (Example 7). Kirpotin also teaches that if necessary, to achieve an osmolarity of 377 mmole/kg, sucrose could be added to the medium (Example 8). The liposomes contain hydrogenated egg phospholipid and cholesterol. Doxorubicin is loaded into the preformed liposomes (Example 7).

The use of sucrose and the ammonium sulfate and sucrose together in the hydrating medium in the teachings of Forssen, Wong, and Mammarella with a

reasonable expectation of success since Kirpotin teaches the use of sucrose along with ammonium sulfate to achieve an osmolarity of 377 mmole/kg.

The reference of Hu (US 2005/0129750 is cited of interest.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore /
Primary Examiner, Art Unit 1612

GSK